transforming factor *neu*, hepatocyte growth factor, retinoic acid, glucocorticoids, and nuclear factor-κB. The overexpressed NGAL protein binds to MMP-9, thereby preventing MMP-9 degradation and increasing MMP-9 enzyme activity. In turn, MMP-9 activity promotes cancer progression by degrading the basement membranes and extracellular matrix, liberating VEGF, and thus enabling angiogenesis, invasion, and metastasis. Paradoxically, recent studies in several tumor cell lines have shown that NGAL enhanced the epithelial phenotype, reduced tumor growth, and suppressed metastasis; this prosurvival activity of NGAL is mediated by its ability to bind and transport iron inside the cells.[9] Especially pertinent to the study by Porta *et al.*[3] are recent findings that (1) NGAL is induced by hypoxia and may indeed be driven by the pro-neoplastic hypoxia-inducible factor-1α (HIF-1α), which in turn is regulated by *VHL*; (2) NGAL can inhibit HIF-1α; and (3) NGAL can inhibit VEGF synthesis.

How does one reconcile the seemingly contradictory roles of NGAL in human biology? A potentially unifying hypothesis is offered in Figure 1. Efficient mechanisms have evolved for the intracellular uptake of NGAL via receptors such as megalin, and for intracellular trafficking via endosomes. The subsequent molecular path taken by NGAL may be largely dependent on the type of molecule it is complexed with. NGAL that is devoid of siderophore and iron (holo-NGAL) rapidly scavenges intracellular iron. The resultant intracellular iron depletion results in a decrease in the mammalian cell's proliferative ability and in induction of apoptosis. On the other hand, when NGAL is bound to siderophore and iron, there is a rapid release of iron with regulation of iron-dependent molecular pathways and downstream induction of proliferation and epithelial transformation. Finally, when NGAL is complexed with MMP-9 instead, there is enhancement of the active MMP-9 pool with resultant upregulation of MMP-9's well-known proangiogenic and proinvasive properties. Future studies aimed at further testing these hypotheses hold promise for advancing our understanding of tumor biology, and for potentially validating NGAL as a biomarker for personalizing renal cancer care.

DISCLOSURE

PD is a co-inventor on patent applications covering the use of NGAL as a biomarker of acute and chronic kidney diseases, and has received honoraria from Abbott Diagnostics and Biosite Inc.

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LECT2 amyloidosis

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LECT2 amyloidosis is the latest systemic type of amyloidosis to be described. It was discovered in patients with nephrotic syndrome and renal failure and is characterized by amyloid deposition in glomeruli, renal vessels, and interstitium. Clinical and pathological features of earlier phases of this type of amyloidosis have yet to be determined.

Kidney International (2010) **77,** 757–759. doi:10.1038/ki.2010.18

In 1971 Glenner *et al.* reported the amino acid structure of monoclonal immunoglobulin light chain (AL) protein isolated from tissues of a patient with primary amyloidosis.[1] This was the first human amyloid protein to be chemically characterized. Structural characterization of human secondary amyloid protein (serum amyloid A (SAA)) was soon to follow in 1972,[2] and since then, eight additional proteins associated with human systemic amyloidosis have been identified, for a total of ten (Table 1). The latest of these amyloid proteins is leukocyte chemotactic factor 2 (LECT2), which, so far, appears mainly to cause renal amyloidosis.[3]

LECT2 amyloid was originally discovered in a patient who had nephrotic syndrome and slowly progressive renal failure over a number of years (Figure 1). Clinical evaluation and renal biopsy studies failed to determine the type of amyloidosis, and only when the patient developed renal-cell carcinoma, which necessitated nephrectomy, did amyloid-laden tissue become available for biochemical analysis. Without this chain of events and the inquisitive mind of the renal pathologist, it is unlikely that the correct diagnosis for this patient would have been made, and LECT2

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Table 1 | Human systemic amyloidosis proteins

Fibril proteins	Year protein structure characterized
Immunoglobulin light chain (AL)	1971
Amyloid A (AA)	1972
Transthyretin	1981
Cystatin C	1986
Apolipoprotein A-I	1988
Gelsolin	1990
Fibrinogen Aα-chain	1993
Lysozyme	1993
Apolipoprotein A-II	2001
LECT2	2008

amyloidosis would have remained unknown for some longer period of time. At first it appeared that this first case might be an isolated phenomenon and not of significant importance in clinical nephropathology. Now that we have seen additional cases, and in light of the report by Larsen *et al.*[4] (this issue), we can project that LECT2 amyloidosis will be an important entity to consider in seeking a diagnosis for renal disease. This is a good time for us to take a few minutes and contemplate what we do know and what we do not know about this newly discovered type of amyloidosis.

First we should realize that LECT2 has been discovered in cases of renal amyloidosis in which no definitive diagnosis had been made for extended periods of time. The first couple of patients to come to our attention had had nephrotic syndrome for at least 2 years, and renal biopsies displayed advanced amyloid deposition. The original report and the report by Larsen *et al.*[4] point out what appear to be distinguishing histological features for LECT2 amyloidosis, namely, prominent congophilia and involvement of not only glomeruli but also vascular and interstitial structures. This is probably not the case for early stages of the disease. One question that we need to address as we accumulate more cases is whether glomerular basement membrane deposition occurs first or whether there is substantial amyloid deposition in blood vessel walls and/or interstitial deposition early in the course of the disease. This will be important if we are to accurately evaluate renal biopsies and make a timely diagnosis for patients with this type of amyloidosis.

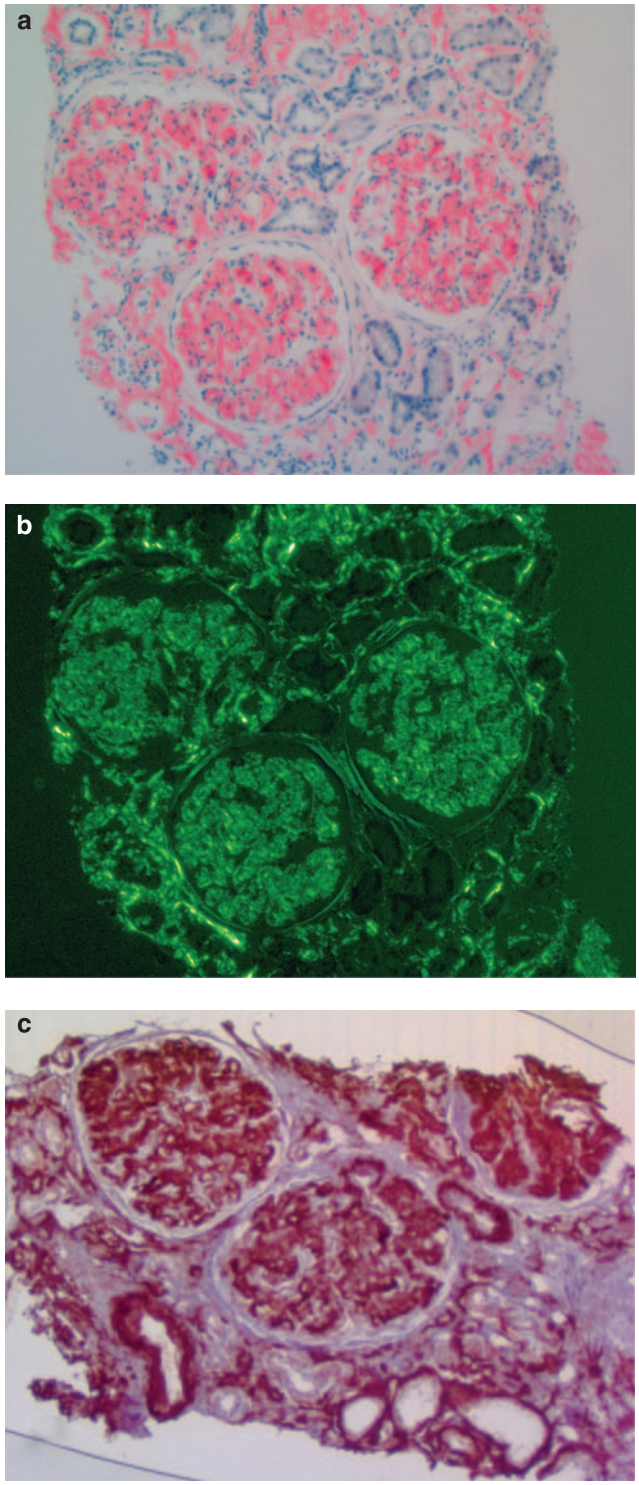

Figure 1 | Renal histology of LECT2 amyloidosis. (**a**) Renal biopsy from a patient with LECT2 amyloidosis, showing amyloid deposits in glomeruli, blood vessel walls, and tubular interstitium. (Congo red stain; originval magnification, ×100.) (**b**) Same section as in panel **a**, viewed between cross-polars, showing characteristic green birefringence of amyloid. (**c**) Immunohistochemical staining of renal biopsy in panel **a**, stained with anti-LECT2 antibody by an antigen retrieval technique at pH2. It should be noted that although immunohistochemistry for LECT2 was originally described for sections from frozen tissue, formalin-fixed, paraffin-embedded tissue may require antigen retrieval techniques to give positive staining.

Another question is whether LECT2 amyloidosis is strictly a renal disease or is similar to fibrinogen Aα-chain hereditary amyloidosis, in which renal pathology is paramount, but liver, spleen, and even cardiac amyloid deposition may be seen in later stages, especially if the patient's life is extended by renal dialysis. As the story of LECT2 amyloidosis evolves, it will be necessary to observe the rate of progression of the renal pathology. For a disease for which there is no specific therapy, will there be a place for renal transplantation, such as with apolipoprotein A-I amyloidosis, where organ transplantation can give a meaningful extension of life?

Like all proteins associated with systemic amyloidosis, except for SAA, LECT2 was well characterized before its discovery as an amyloid fibril precursor protein. As its name indicates, LECT2 was discovered in studies searching for proteins with leukocyte chemotactic activity.[5] It was also discovered independently as a factor that may be important in restructuring of cartilage and, therefore, was named chondromodulin.[6] LECT2 has now been accepted as the official name, although further studies on possible biological properties of the protein suggest that LECT2 may be a misnomer. Actually, the word 'amyloid' is a misnomer, but we have all learned to live with this designation. The true biological function of LECT2, if there is one, has yet to be determined. While it has leukocyte chemotactic activity *in vitro* and may be involved in tissue repair, additional studies have suggested that LECT2 may be involved in autoimmune response functions, and structure homology studies suggest a possible endopeptidase function.[7–9] Reports of LECT2 induction in association with hepatocellular tumors raise the question of whether other neoplastic processes, such as renal-cell carcinoma, can play a role in the pathogenesis of LECT2 amyloidosis.[10]

The pathogenesis of LECT2 amyloidosis remains to be elucidated. All forms of amyloidosis are protein folding deposition diseases, and a number of factors may be at play in the formation and deposition of amyloid fibrils. First it is necessary to have a substrate in sufficient abundance to form clinically significant fibril deposits. This is a determining factor in AL amyloidosis, in which monoclonal immunoglobulin light chains are the result of a plasma-cell dyscrasia. In AA amyloidosis, increased levels of SAA are induced by an inflammatory response and, in susceptible people, lead to amyloidosis. In the hereditary forms of amyloidosis, genetically determined variant forms of plasma proteins are the cause of fibril formation. Although there is no evidence that LECT2 amyloidosis is an inherited condition, it is of interest that the report by Larsen *et al.*[4] indicates that four of seven cases identified as LECT2 were in Hispanic subjects. The first two cases identified in our Amyloid Research Laboratories were in patients of Hispanic origin. Therefore, although no obvious genetic factor has been identified, there may be some genetic predisposition for this type of amyloidosis. For LECT2 there is presently little basis to formulate hypotheses on pathogenesis. LECT2 is synthesized principally by the liver, and it has been shown that increased expression of LECT2 may occur with hepatocellular tumors. It is not yet obvious whether increased expression of LECT2 is a major factor in amyloid formation or whether some biological factor involved in the metabolism of LECT2 is the instigating factor in the initiation of fibril formation. The predilection for renal involvement suggests the importance of local tissue factors for amyloid fibril deposition, but the characteristic appearance of deposits in the glomerular basement membrane, the walls of blood vessels, and the tubular interstitium suggests that amyloid deposition may be more widespread and involve other organs. Future postmortem studies may clarify this issue. The structure of an amyloid protein obviously is important in forming β-fibrils. LECT2 is postulated to have extensive β-structure, as do transthyretin and immunoglobulin light chain. Since the entire LECT2 protein was found in the fibrils that have been analyzed to date, it is unlikely that proteolytic degradation is necessary for fibril formation. It is possible, however, that interference in a catabolic pathway for LECT2 could lead to increased local tissue levels of LECT2 and that this could lead to the initiation of fibril formation and deposition.

It is always exciting to identify the basis of any disease and to be able to see how knowledge of its pathogenesis evolves.

DISCLOSURE

The author declared no competing interests.

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